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FAY SHARPE LLP
1228 Euclid Avenue, 5th Floor
The Halle Building
Cleveland, OH 44115

EXAMINER
TON, THAIAN N

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KARL TRYGGVASON,
SERGEY RODIN, and ANNA DOMOGATSKAYA

Appeal 2016-001857
Application 12/725,877
Technology Center 1600

Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving a composition and method for enabling self-renewal of pluripotent human stem cells grown *in vitro*. The Examiner rejected the claims as anticipated, as obvious, as non-statutory subject matter, and on the grounds of obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the Real Party in Interest as the Biolamina AB (*see* App. Br. 1).

Statement of the Case

Background

"A stem cell is an undifferentiated cell from which specialized cells are subsequently derived. Embryonic stem cells possess extensive self-renewal capacity and pluripotency with the potential to differentiate into cells of all three germ layers" (Spec. ¶ 3). "[T]he development of chemically defined and xeno-free culture environments for human embryonic stem (hES) cells has been an important goal" (Spec. ¶ 7).

"The present disclosure is directed to the development of compositions, such as extracellular matrices, and processes for using the same, for culturing human stem cells *in vitro* in an undifferentiated state" (Spec. ¶ 15).

The Claims

Claims 1–12 and 14–19 are on appeal. Claim 1 is representative and reads as follows:

> 1. A composition for enabling self-renewal of pluripotent human stem cells grown *in vitro,* comprising:
>
> a substrate;
>
> a coating comprising intact recombinant laminin-511 (LN-511 or laminin-10) and being devoid of both animal proteins and feeder cells; and
>
> a chemically defined medium that is devoid of feeder cells and contains bFGF.

The Issues

A. The Examiner rejected claims 1, 2, 14, 15, and 17–19 under 35 U.S.C. § 102(b) as anticipated by Tryggvason '401[2] as evidenced by Doi[3] (Final Act. 6).

B. The Examiner rejected claims 1–12 and 14–19 under 35 U.S.C. § 103(a) as obvious over Beattie,[4] Millipore,[5] Kikkawa,[6] and Ludwig[7] (Final Act. 7–10).

C. The Examiner rejected claims 1–12 and 14–19 under 35 U.S.C. § 103(a) as obvious over Miyazaki[8] and Ludwig (Final Act. 10–11).

D. The Examiner rejected claims 1, 3, 5–12, 14, 16, 18, and 19 under 35 U.S.C. § 103(a) as obvious over Tryggvason '401, Doi, and Ludwig (Final Act. 11–13).

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[2] Tryggvason et al., WO 2008/084401 A1, published July 17, 2008 ("Tryggvason '401").
[3] Doi et al., *Recombinant Human Laminin-10 (α5β1γ1)*, 277 J. BIOLOGICAL CHEMISTRY 12741–48 (2002) ("Doi").
[4] Beattie et al., *Activin A Maintains Pluripotency of Human Embryonic Stem Cells in the Absence of Feeder Layers*, 23 STEM CELLS 489–95 (2005) ("Beattie").
[5] Millipore catalog, Human Laminin (pepsinized) Purified Protein, Accessed Feb. 24, 2009 ("Millipore").
[6] Kikkawa et al., *Laminin isoforms differentially regulate adhesion, spreading, proliferation, and ERK activation of β1 integrin-null cells*, 300 EXPERIMENTAL CELL RESEARCH 94–108 (2004) ("Kikkawa").
[7] Ludwig et al., *Derivation of human embryonic stem cells in defined conditions*, 24 NATURE BIOTECHNOLOGY 185–7 (2006) ("Ludwig").
[8] Miyazaki et al., *Recombinant human laminin isoforms can support the undifferentiated growth of human embryonic stem cells*, 375 BIOCHEMICAL BIOPHYSICAL RESEARCH COMMUNICATIONS 27–32 (2008) ("Miyazaki").

E. The Examiner rejected claims 1, 2, 4–6, 9, 11, 13–15, and 17–19 on the ground of nonstatutory double patenting as being unpatentable over claims 1–3 of US 8,722,405 (Final Act. 14–15).

F. The Examiner rejected claims 1–4 under 35 U.S.C. § 101 as directed to a judicial exception (Ans. 3–7).

A., C., D. 35 U.S.C. § 102(b) and 103(a) over Tryggvason '401 or Miyazaki

Because the same priority issue is dispositive for these four rejections, we will consider them together.

The Examiner finds "the priority document (11/969,620) does not have support for the phrase 'a coating comprising *intact* laminin' (claim 1); or 'a substrate comprising *full-length* recombinant laminin' (claim 5)" (Ans. 7). In particular, the Examiner finds the "phrase laminin can encompass any number of fragments of laminin, which may include full-length or intact laminin, but does not exclude the possibility of fragments that are not full length or intact" (Ans. 8).

Appellants contend

> the '620 application provides at least implicit support for a laminin that is "intact" or "full-length". Initially, paragraph [0008] of the '620 application describes laminins as being large transparent extracellular matrix proteins that are composed of three chains. Throughout the text, reference is made only to "laminins", with no reference to various parts of the laminin. . . . Finally, claim 1 of the '620 application refers to "a coating comprising laminin 332 or laminin 511, or their functional

> domains." The phrase "or their functional domains" also emphasizes that "laminin" refers to the complete protein.

(App. Br. 4–5).

The issue with respect to these rejections is: Does the evidence of record support the Examiner's conclusion that the Specification of US 11/969,620 fails to provide descriptive support for the phrase "intact laminin" or "full-length laminin" in claims 1 and 5?

Findings of Fact

1. The Specification of US 11/969,620 teaches "[l]aminins are large trimeric extracellular matrix proteins that are composed of alpha, beta, and gamma chains. There exist five different alpha chains, three beta chains and three gamma chains that in mouse and human tissues have been found in at least fifteen different combinations" (US 11/969,620 Spec. ¶ 8; *cf.* US 60/883,406 ¶ 6).

2. The Specification of US 11/969,620 teaches "[t]hese molecules are termed laminin-1 to laminin-15 based on their historical discovery, but an alternative nomenclature describes the isoforms based on their chain composition, e.g. laminin-111 (laminin-1) that contains alpha-1, beta-1 and gamma-1 chains" (US 11/969,620 Spec. ¶ 8; *cf.* US 60/883,406 ¶ 6).

3. The Specification of US 11/969,620 teaches:

> 96-well tissue cell culture plates (Sarstedt) were coated overnight at 4°C by sterile solutions of extracellular matrix proteins: murine laminin-111 (Invitrogen), human recombinant laminin-332, human recombinant laminin-411 (Kortesmaa, J., Yurchenco, P., and Tryggvason, K. (2000); Recombinant laminin-8 (alpha(4)beta(1)gamma(1)). Production, purification, and interactions with integrins. J Biol Chem *275,* 14853-14859, U.S. Patent 6,638,907), human recombinant laminin-

> 511 (Doi, M., Thyboll, J., Kortesmaa, J., Jansson, K., livanainen, A., Parvardeh, M., Timpl, R., Hedin, U., Swedenborg, J., and Tryggvason, K. (2002); Recombinant human laminin-10 (alpha5beta1gamma1); Production, purification, and migration-promoting activity on vascular endothelial cells. J Biol Chem *277,* 12741-12748; U.S. Patent 6,933,273)

(US 11/969,620 Spec. ¶ 31; *cf.* US 60/883,406 ¶ 22).

4. The Specification of US 11/969,620 claims "1. A composition for enabling proliferation of pluripotent stem cells grown *in vitro* on a coating comprising laminin 332 (laminin-5) or laminin 511 (laminin-10), or their functional domains" (US 11/969,620 Spec. 15, claim 1; *cf.* US 60/883,406 12, claim 1).

Principles of Law

Under 35 U.S.C. § 120, "in a chain of continuing applications, a claim in a later application receives the benefit of the filing date of an earlier application so long as the disclosure in the earlier application meets the requirements of 35 U.S.C. § 112, ¶ 1, including the written description requirement, with respect to that claim." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326 (Fed. Cir. 2008).

Analysis

We find that Appellants have the better position. The Specification of US 11/969,620 is reasonably interpreted as referring to laminin proteins composed of intact, full-length alpha, beta, and gamma chains for two reasons. First, the original claim expressly recites particular laminins "or their functional domains" (FF 4). The most reasonable interpretation of "or their functional domains" is that the original claim is drawn to particular

laminins that are full-length and intact and may also encompass laminins that are not full-length and intact, but rather are composed of "functional domains" of the laminins.

Second, the description in paragraph 31 of the actual laminins used in examples (FF 3) cites to the use of recombinant laminins produced in several papers published in the Journal of Biological Chemistry. A review of those papers shows that the laminins produced in those papers are full-length and intact, further supporting the conclusion that the Specification has "set forth enough detail to allow a person of ordinary skill in the art . . . to recognize that the inventor invented what is claimed." *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928 (Fed. Cir. 2004).

We therefore reverse the Examiner's rejections that rely upon either Tryggvason '401 or Miyazaki, because these references are not prior art relative to the priority date of the US 11/969,620 priority document filed Jan. 4, 2008, and provisional US 60/883,406, filed Jan. 4, 2007, both of which reasonably provide descriptive support for full-length, intact laminins.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that the Specification of US 11/969,620 fails to provide descriptive support for the phrase "intact laminin" or "full-length laminin" in claims 1 and 5.

B. 35 U.S.C. § 103(a) over Beattie, Millipore, Kikkawa, and Ludwig

The Examiner finds "Beattie teach[es] culturing human ES cells . . . on laminin in DSR medium containing 50 ng/ml of recombinant activin A and 50 ng/ml recombinant KGF and 10 mM NIC" (Final Act. 8). The

Examiner acknowledges that Beattie does not teach "the medium is a chemically defined medium that is devoid of feeder cells" (*id.*).

The Examiner finds "Ludwig teach the development of TeSR1, a serum-free, animal product-free medium that supports culture and derivation of human ES cells" (Final Act. 9). The Examiner finds the ordinary artisan "would have been motivated to use the TeSR1 media because it would prevent contamination from animal products" (Final Act. 10).

The issue with respect to these rejections is: Does the evidence of record support the Examiner's conclusion that Beattie, Millipore, Kikkawa, and Ludwig render claims 1 and 5 obvious?

Findings of Fact

5. Beattie teaches

> passage 43 hESCs [human embryonic stem cells] were cultured on dishes coated with laminin . . . in the presence of CM [conditioned medium] from mEFs [mouse embryonic feeder layers] supplemented with 10 ng/ml basic fibroblast growth factor . . . or on laminin in DSR [serum replacement] medium containing 50 ng/ml human recombinant activin A, 50 ng/ml human recombinant KGF (both from PreproTech), and 10 mM NIC

(Beattie 490, col. 1).

6. Beattie teaches "[r]emoval of activin from the growth medium resulted in the rapid change in cell morphology to a differentiated phenotype" (Beattie 492, col. 1).

7. Beattie teaches "[t]hese data show that maintenance of hESCs in medium containing activin A allows the maintenance of pluripotency

without the need for coculture with other foreign or human cells" (Beattie 495, col. 1).

8. Beattie teaches "[i]n contrast, when activin was removed from the culture for 1 week, the level of expression was reduced to 3.9%" (Beattie 492, col. 1).

9. Ludwig teaches "feeder-independent human ES cell culture that includes protein components solely derived from recombinant sources or purified from human material. We describe the derivation of two new human ES cell lines in these defined culture conditions" (Ludwig, abstract).

10. Ludwig teaches "a combination of collagen IV, fibronectin, laminin and vitronectin supported robust, long-term proliferation of human ES cells in TeSR1" (Ludwig 186, col. 1).

11. Ludwig teaches that "TeSR1 containing all five factors (bFGF, LiCl, GABA, pipecolic acid and TGFβ) is sufficient to support feeder-independent human ES cell culture as well as or better than fibroblast-conditioned medium" (Ludwig 186, col. 2).

12. Ludwig teaches:

> Unlike previous human ES cell culture media that included proprietary, poorly defined serum components with undisclosed formulations, all TeSR1 components are disclosed, and thus should serve as a starting point for further optimization by other investigators. One of the areas that needs improvement is the matrix, as the purified human matrix components are expensive and provide a potential route of contamination by human pathogens.

(Ludwig 186, col. 2).

Principles of Law

"The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Analysis

We agree with the Examiner that the claims are obvious over the combination of Beattie, Millipore, Kikkawa, and Ludwig. In particular, Beattie teaches a composition that comprises a substrate, dishes, with a laminin coating devoid of other proteins and feeder cells and a medium that containing bFGF (FF 5). As the Examiner acknowledges, Beattie does not teach a defined chemical medium devoid of feeder cells (*see* Final Act. 8). However, Ludwig teaches defined chemical media for growth of ES cells that includes bFGF (FF 9, 11) grown on a matrix containing laminin and other proteins (FF 10).

We agree that the ordinary artisan, interested in improving the composition of Beattie to use defined serum components, would have had reason to employ a serum composition as suggested by Ludwig (FF 12).

Appellants contend that "Ludwig's medium does not contain activin A, and thus Beattie would not have used Ludwig's medium" (App. Br. 7). Appellants contend "Beattie actually teaches away from Ludwig, as Beattie teaches that media conditions excluding activin would result in differentiated cells, and Ludwig's medium does not contain activing[]" (*id.*).

We do not find this argument persuasive because claims 1 and 5 utilize the open transitional language "comprising" and are therefore open to

chemically defined medium that comprise bFGF, all of the components disclosed in Ludwig, and purified recombinant activin A disclosed by Beattie. That is, to the extent that Beattie suggests activin A is a required element in the growth medium, Ludwig does not teach away from inclusion of this purified protein and claims 1 and 5 do not exclude the presence of activin A. Appellants do not identify, and we do not find, any teaching in either Beattie or Ludwig criticizing, discouraging, or discrediting the use of defined medium that contains activin A along with the specific components disclosed by Ludwig (FF 11).

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Beattie, Millipore, Kikkawa, and Ludwig render claims 1 and 5 obvious.

E. Double Patenting

Appellants stated "Applicants do not appeal this rejection, and will overcome this rejection by submitting a Terminal Disclaimer" (App. Br. 8). We therefore summarily affirm the obviousness-type double patenting rejection. *See* Manual of Patent Examining Procedure § 1205.02 ("If a ground of rejection stated by the examiner is not addressed in the appellant's brief, that ground of rejection will be summarily sustained by the Board.")

F. 35 U.S.C. § 101

The Examiner finds:

> The claim(s) are directed to a composition of matter (Step 1), a composition comprising 1) a substrate; 2) a coating comprising intact recombinant laminin-511; 3) chemically defined medium and 4) bFGF. Further embodiments recite that the medium comprises growth factors (claim 2); human albumin (claim 3). This composition of matter is directed to a natural phenomenon

(Ans. 5). The Examiner finds "the limitations of the claims do not impose limits on the claim scope to render the claims markedly different in structure from a naturally occurring product" (Ans. 6).

Appellants contend "[t]hese methods can only be practiced due to the non-naturally occurring elements, i.e. the substrate, the non-natural coating formed from the laminin, and the chemically defined medium. Thus, the claims, which contain additional elements, amount to 'significantly more' than the judicial exception itself" (Reply Br. 3). Appellants contend that

> claim 1 is quite similar to claim 5 of Example 17 of Appendix 2 of the *July 2015 Update: Subject Matter Eligibility* (i.e. Example 9 of the *Examples: Nature-Based Products* issued on December 16, 2014) . . . claim 5 was found to be eligible because the combination of the cells in the scaffold confined the claim to a particular useful application (repair of cardiac tissue), and improved the technology.

(Reply Br. 3–4).

We find that Appellants have the better position. In Example 9 of the 2014 Guidance for nature-based products,[9] claim 1 is drawn to an isolated

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[9] https://www.uspto.gov/patents/law/exam/mdc_examples_nature-based_products.pdf 1–17 ("2014 Guidance").

cell while claim 5 is drawn to a combination of the cells with a scaffold (2014 Guidance 14). The 2014 Guidance states the

> recitation of the biocompatible three-dimensional scaffold in combination with the pacemaker cells is not required for growing or using the cells, because the cells can be grown or used in other containers, and is not recited at a high level of generality. The addition of the pacemaker cells to the scaffold confines the claim to a particular useful application of the scaffold.

(2014 Guidance 15).

The instant claims are similar to Example 9 because the pluripotent human stem cells are not recited as growing on any substrate, but rather a particular substrate coated with intact recombinant laminin-511 along with a chemically defined medium (*see* claims 1 and 5).

We agree with Appellants that the claimed combination results in something "significantly more" than the naturally occurring products. This is not a simple combination of known rhizobium bacterial inoculant components as in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 132 (1948). Nor is this drawn to a specific biological product such as the nucleic acid at issue in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116–2117 (2013).

Instead, the claims require a purified natural product, laminin-511 coated onto a substrate without other components, and also requires a chemically defined medium solution that comprises bFGF but lacks feeder cells. This claimed product, not naturally occurring, enables pluripotent stem cells to grow *in vitro* without differentiation, thereby adding something "significantly more" than the simple combination of components which, if

simply mixed together, would not necessarily result in a composition capable of supporting the growth of pluripotent stem cells.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Beattie, Millipore, Kikkawa, and Ludwig. Claims 2–12 and 14–19 fall with claim 1.

We affirm the rejection of claims 1, 2, 4–6, 9, 11, 13–15, and 17–19 on the ground of nonstatutory double patenting as being unpatentable over claims 1–3 of US 8,722,405.

We reverse the rejection of claims 1, 2, 14, 15, and 17–19 under 35 U.S.C. § 102(b) as anticipated by Tryggvason '401 as evidenced by Doi.

We reverse the rejection of claims 1–12 and 14–19 under 35 U.S.C. § 103(a) as obvious over Miyazaki and Ludwig.

We reverse the rejection of claims 1, 3, 5–12, 14, 16, 18, and 19 under 35 U.S.C. § 103(a) as obvious over Tryggvason '401, Doi, and Ludwig.

We reverse the rejection of claims 1–4 under 35 U.S.C. § 101 as directed to a judicial exception.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED